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# Myocardial injury and its prevention in the perioperative setting

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In the UK, there are ~20 000 deaths within 30 days of surgery every year, 9000 of which have a cardiac cause.[93] The number of major cardiac complications is likely to be in the region of 150 000 per annum. As 60% of patients who die within 30 days of surgery suffer from coronary artery disease[94] it is reasonable to assume that the majority of cardiac complications of anaesthesia and surgery results from myocardial ischaemia leading to myocardial injury (Fig. 1).

## Myocardial responses to ischaemia

### *Acute myocardial ischaemia*

The acute occlusion or progressive constriction of a coronary artery causes reduction or abolition of systolic shortening and thickening of the ischaemic wall.[81] Ischaemic segments also demonstrate paradoxical wall motion (termed post-systolic shortening or post-systolic thickening). These functional changes relate directly to the severity of the reduction in coronary blood flow. As post-systolic shortening and thickening occur after aortic valve closure, they do not contribute to ejection and result in an internal shift of blood in the ventricle, and may impair relaxation. Acute or progressive ischaemia of the left ventricle also cause an increase in chamber stiffness in the ischaemic and in remote non-ischaemic segments.[81] This generalized increase in myocardial chamber stiffness contributes to an elevation of the left ventricular end-diastolic pressure, especially in the presence of volume loading.[81] The increase in end-diastolic pressure contributes to a vicious circle as it further impairs coronary blood flow by increasing diastolic wall tension. The mechanisms of the increase in ventricular chamber stiffness of remote, well-perfused myocardium have not been elucidated. However, ventricular stiffening does not depend on loading conditions and is likely to result from the release of mediators.

#### *Mechanisms of myocardial ischaemia*

The time-course of the effects of ischaemia on cardiac tissue is well known. There is a marked reduction of contractile function resulting from decreased ATP production a few seconds after the onset of ischaemia. Leakage of potassium ions is responsible for the alterations of ST-segments. Within minutes, an intracellular acidosis develops associated with an increase in myoplasmic $Ca^{2+}$ and the beginning of cell swelling. Later, cellular lesions become irreversible. The ultrastructure of the cells becomes altered and macromolecules (CK-MB, troponins) are released. An increased concentration of cytosolic and mitochondrial $Ca^{2+}$ plays a central role in the damage to the cells and their membranes[104] (Fig. 2).

Myocardial ischaemia occurs in the presence of fixed or dynamic coronary artery stenoses and, in the case of the right ventricle, in response to afterload mismatch. The main causes of ischaemia with fixed coronary stenoses include tachycardia, excessive left ventricular filling, and hypoxaemia. Tachycardia, systolic hypertension and β-adrenergic stimulation increase the oxygen requirements and may decrease oxygen delivery. Causes of ischaemia in the presence of dynamic stenoses include those described above and, in addition, activation of sympathetic and parasympathetic systems. Moreover, several endothelium-derived mediators may enhance vasoconstriction.

In the normal heart, the role of the autonomic nervous system is overshadowed by local metabolic coronary vasoregulation. Normally, activation of the sympathetic

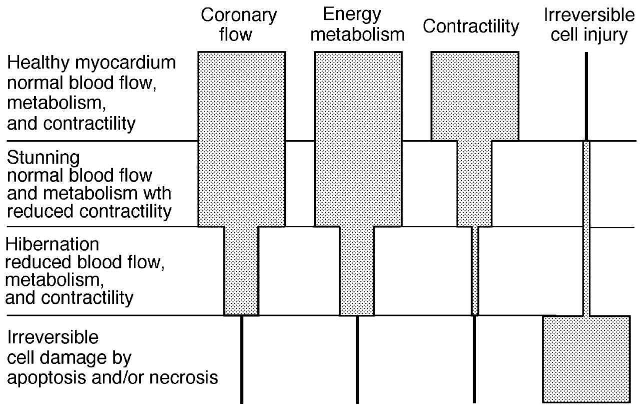


**Fig 1** Schematic characterization of cardiac 'stunning' and 'hibernation'. In stunning normal blood flow and energy metabolism are accompanied by reduced contractility, designated as 'flow-contractility mismatch'. The impaired contractile function seems to be caused primarily by increased intracellular $Ca^{2+}$, activation of $Ca^{2+}$-dependent non-lysosomal cysteine proteinases (calpains), and degradation of sarcomere-associated proteins including troponin-I. Hibernation is characterized by reduced contractility accompanied by reduced oxygen consumption as a consequence of reduced blood flow. Partially damaged cardiomyocytes can be rescued to full function after stunning as well as after hibernation, provided normal blood flow is restored after the latter within the critical time period before irreversible cell damage has occurred. Despite their distinct definition, stunning and hibernation may merely represent intermediary states in a continuum extending from unimpaired functional myocytes to necrosis.[157]

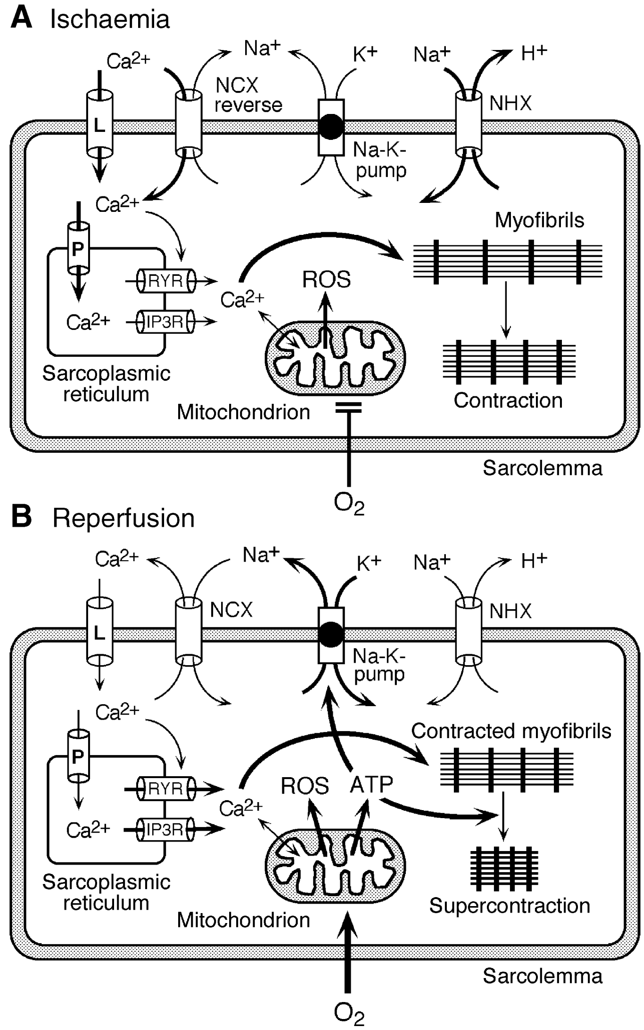


**Fig 2** Changes and consequences of cation fluxes during ischaemia-reperfusion. (A) Cessation of oxygen supply in ischaemia leads to a loss of ATP production and an increase of reactive oxygen species (ROS) in the mitochondria. Reduced activity of the ATP consuming $Na^{+}$-$K^{+}$-pump lowers the outside–inside sodium gradient, $Na^{+}$ accumulates in the myocyte and the resting membrane potential is lowered. With the development of acidosis, the $Na^{+}$-$H^{+}$-exchanger (NHX) further increases intracellular $Na^{+}$. Under these conditions the $Na^{+}$-$Ca^{2+}$-exchanger (NCX) operates in the reverse mode, letting $Ca^{2+}$ into the cell. $Ca^{2+}$ also enters through the sarcolemmal L-type voltage-gated $Ca^{2+}$-channel (L) as the resting membrane potential is low. The increased $Ca^{2+}$ is taken up into the sarcoplasmic reticulum (SR) by the SR $Ca^{2+}$-pump SERCA2 (P) and released from there via two types of release channels, the ryanodine receptor channel (RYR) and the IP3 receptor channel (IP3R), leading to contraction. (B) Reoxygenation during reperfusion restores ATP production with a further boost of ROS. Reactivation of the $Na^{+}$-$K^{+}$-pump by ATP slowly restores the sodium gradient leading to normal cation fluxes with the NCX eventually extruding the excess of cytosolic $Ca^{2+}$. During the early reperfusion phase when the intracellular $Ca^{2+}$ level is still high, myocardial contracture (supercontraction of myocytes) may develop. When contracture affects the entire heart as it may occur after global ischaemia, it has been termed the 'stone heart' phenomenon.[104 157]

nervous system at the level of $\alpha_1$- and $\beta_1$-adrenoceptors increases blood pressure, heart rate, and contractility. As a result, myocardial oxygen consumption increases and local vasoregulation decreases coronary vascular resistance. The direct effect of $\alpha_1$-adrenoceptor stimulation, vasoconstriction, is minimal under normal circumstances but may be exaggerated in the presence of coronary artery disease, extreme exercise, or haemorrhagic shock. Activation of the parasympathetic system causes bradycardia and hypotension, thereby reducing myocardial oxygen requirements. Local regulation increases coronary vascular resistance and the direct coronary vasodilatation caused by acetylcholine is masked.

Endothelins act on vascular smooth muscle and are extremely powerful vasoconstrictors. However, they exert complex physiological effects. Through activation of endothelin B ($ET_B$)-receptors, endothelial nitric oxide synthase is activated and nitric oxide is released causing cGMP-mediated vasodilatation. Activation of $ET_B$-receptors also increases the activity of cyclo-oxygenase leading to the release of prostaglandin $I_2$ ($PGI_2$). The latter causes vasodilatation and minimizes smooth muscle cell proliferation. When the endothelium is normal, there is a delicate balance between vasoconstriction and vasodilatation in response to endothelins. The vasodilatory role of the endothelium becomes more apparent when it is damaged by atheroma, hypercholersterolaemia, hypertensive heart disease, and after reperfusion. An imbalance of mediators can then develop and facilitate vasoconstriction. There are several important mechanisms involved in this vasoconstriction. Norepinephrine causes $\alpha_1$-adrenoceptor-mediated vasoconstriction. When the endothelium is damaged, acetylcholine causes muscarinic receptor mediated vasoconstriction,[79] instead of endothelium-dependent vasodilatation. Thus, with endothelial damage both sympathetic and parasympathetic stimulation may cause coronary vasoconstriction. As sympathetic overactivity is part of the perioperative stress response, exaggerated vasoconstriction may be expected to contribute to perioperative myocardial ischaemia and cardiac damage. Similarly, the effects of endothelins are altered when the endothelium is damaged and activation of nitric oxide-synthase and cyclo-oxygenase does not occur. Consequently, only effects of endothelins in these circumstances are those on endothelin A ($ET_A$)- and $ET_B$-receptors in vascular smooth muscle resulting in vasoconstriction and smooth muscle proliferation.

## *Myocardial stunning (flow-contractility mismatch)*

The term myocardial stunning was coined by Braunwald and Kloner[14] in 1982 to describe a reduction in function after a brief period of ischaemia followed by reperfusion. The impairment of function could last for several hours or days at a time when coronary blood flow was normal and there was no obvious cellular damage. In clinical practice, interventions such as transluminal coronary angioplasty, coronary artery bypass graft surgery, and thrombolysis after myocardial infarction are human models of ischaemia-reperfusion phenomena. During the perioperative period, a high proportion of adult patients suffer from episodes of myocardial ischaemia, most of which are silent but can be prolonged. Importantly, silent myocardial ischaemia is supposed to be a common cause of myocardial stunning and is a predictor of adverse cardiac outcome.

### *Mechanisms of myocardial stunning*

Myocardial ischaemia followed by reperfusion causes reversible or irreversible damage depending on its duration (Figures 1 and 2). In stunning, ischaemic damage is, in principle, reversible.[67] Three main mechanisms are involved in the establishment of stunned myocardium: formation of free oxygen radicals, accumulation of intracellular $Ca^{2+}$, and degradation of contractile proteins. Many studies have shown that during ischaemia, but more importantly during reperfusion, considerable production of free oxygen radicals occurs.[99] Free radicals do not have a single target, but adversely affect many components of the cell including sarcolemmal and subcellular membranes of organelles. The role of free radicals in stunning is confirmed by the improved post-ischaemic functional recovery in the presence of superoxide dismutase.[138] Production of free radicals involves xanthine oxidase, oxidation of catecholamines, uncoupling of mitochondrial respiration, and activation of neutrophils.

During ischaemia and the early phase of reperfusion, there is an increase in the concentration of intracellular $Ca^{2+}$. Although disappearing in the late phase of reperfusion, $Ca^{2+}$ overload can decrease the sensitivity of contractile proteins to $Ca^{2+}$, thus diminishing the developed force.[9] $Ca^{2+}$ overload my result from altered characteristics of the $Na^+/Ca^{2+}$ antiport and from altered $Ca^{2+}$ fluxes at the level of the sarcoplasmic reticulum. Such alterations in $Ca^{2+}$ handling may be attributable to ischaemia-induced intracellular acidosis. During the early phase of reperfusion, the $H^+/Na^+$ antiport is maximally stimulated. While the acidosis is progressively corrected, there is an increase in intracellular $Na^+$ leading to a further increase in $Ca^{2+}$.

Furthermore there is some evidence that translocation of heat-shock proteins (Hsp-27, αB-crystalline) with covalent binding to myofibrils, together with degradation of contractile proteins such as troponin I, as evidenced in a transgenic mouse model overexpressing troponin I fragments,[88] may be, at least in part, involved in the pathogenesis of myocardial stunning. Also, an increase in coronary vascular resistance and a reduction in vasodilator response were previously reported during reperfusion and may represent some sort of vascular counterparts of stunning in endothelial cells (‘microvascular stunning’).[10] However, not all studies confirm this phenomenon.[32]

## *Myocardial hibernation*

The concept of myocardial hibernation was put forward by Rahimtoola in 1985.[110 111] In the hibernating myocardium, ventricular function is diminished as a consequence of insufficient coronary blood flow (Fig. 1). However, this reduction is not necessarily permanent: an improved balance of supply and demand may augment myocardial function.[7 78] The issue of myocardial hibernation is clinically important because the risk of adverse cardiac outcome in cardiac and non-cardiac surgery increases with a reduction of the ejection fraction. If coronary revascularization increases the ejection fraction the risk of adverse cardiac outcome is likely to be reduced. The likelihood of improved function after coronary reperfusion can be predicted by the result of a dobutamine stress echocardiogram. If dobutamine worsens ventricular function (reversible ischaemia) coronary revascularization is likely to improve cardiac function.[1]

### *Mechanisms of myocardial hibernation*

In hibernating myocardium, cardiac metabolism is down-regulated. It has been proposed that abolition of contractility of hibernating cardiac tissue is attributable to chronic stunning caused by multiple episodes of severe ischaemia followed by repetitive reperfusion. Other experimental models suggest that hibernation occurs as a result of chronic low-flow states. In either case, hibernating myocardium should be salvageable by restitution of an adequate coronary blood flow.

## *Myocardial preconditioning*

In 1986, Reimer and colleagues[112] reported that a brief period of ischaemia decreased the rate of ATP depletion during a further period of ischaemia. Murry and colleagues[89] reported that brief periods of ischaemia made the heart more resistant to infarction during a subsequent acute coronary occlusion, reducing the infarct size by 70–80%. This phenomenon, termed myocardial preconditioning is the most powerful means of achieving cardiac protection. Protection conferred by ischaemic and (most) pharmacological preconditioning protocols exhibits two windows: an acute memory phase that develops within minutes of the ischaemic stimulus and lasts only between 1 and 3 h (classic or early preconditioning), and a longer, more delayed, phase (late preconditioning) starting after 12–24 h and persisting for 2–4 days.[156] Delayed protection by preconditioning is thought to be primarily attributable to alterations in gene expression. Myocardial preconditioning has been documented in all animal species in which it has been studied and in human cardiac tissue. Whether preconditioning facilitates the recovery of function in stunned myocardium is still debated.[19 101] However, delayed preconditioning, in contrast to early preconditioning, always confers protection against stunning.

Preconditioning can result from successive episodes of angina or silent myocardial ischaemia. Indeed, infarct size is known to be smaller, if it has been preceded by angina.[69 91 100] Preconditioning also reduces the risk of ischaemia-induced ventricular tachycardia and ventricular fibrillation.[145] In an almost experimental situation, preconditioning can occur during coronary angioplasty where several temporary occlusions are applied and the effects of a longer period of occlusion are minimized. During coronary angioplasty, sequential occlusions cause less angina, smaller ST-segment changes and lesser lactate production than the first 90 second occlusion.[28] Also, delayed preconditioning can be observed after prolonged nitroglycerin administration in patients undergoing angioplasty 24 h later. Although ischaemic preconditioning, or agents that mimic preconditioning, elicit cardiac protection in patients undergoing cardiac surgery,[51] the clinical use of preconditioning in cardiac surgery is controversial as some studies show benefits[48 148] while others do not,[59 72 102] or even demonstrate deleterious effects.

### *Mechanisms of myocardial preconditioning*

Ischaemic stimuli cause the release of stress mediators such as adenosine, bradykinin, norepinephrine, and opioids. The mechanisms of preconditioning involve several types of triggers and mediators[156] (Fig. 3). Amongst them, adenosine $A_1$- and $A_3$-receptors, bradykinin$_2$-receptors, $\delta_1$-opioid receptors and $\alpha_1$-adrenoceptors play an important role. Via G-proteins, phospholipase C (PLC) and protein kinase C (PKC), these receptors act on mitochondrial and sarcolemmal $K_{ATP}$ channels and $Ca^{2+}$ channels.[152 153] As many mediators are involved in preconditioning, and many

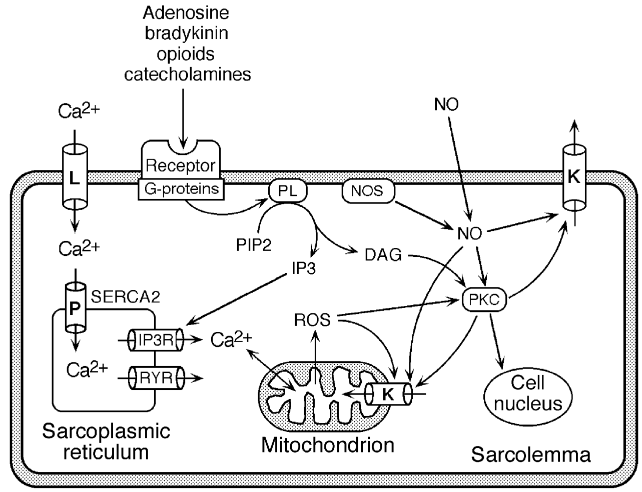


**Fig 3** Main signalling pathways in ischaemic preconditioning. Stimulation of G-protein coupled receptors by primary messengers activates phospholipases (PL), which in turn produce two second messengers originating from phosphatidylinositol bisphosphate (PIP2), namely inositol trisphosphate (IP3) and diacylglycerol (DAG). The former releases $Ca^{2+}$ from the sarcoplasmic reticulum (SR) via the IP3 receptor channel (IP3R), the latter activates different PKC isoforms (PKC). PKC isoforms translocate to their appropriate target sites, activating the sarcolemmal and mitochondrial ATP-dependent potassium channels (K) and initiating distinct gene expression in the cell nucleus. Nitric oxide originating from either the endogenous NO-synthase (NOS) or from extracellular sources may also activate PKC and the potassium channels directly or via its reactive nitrogen oxide products (not shown in this figure). The same mechanism holds true for the reactive oxygen species (ROS) that are produced in the mitochondria under stress and increased $Ca^{2+}$. $Ca^{2+}$ enters the myocyte via the L-type voltage-gated $Ca^{2+}$-channel (L) and is taken up into the SR by the $Ca^{2+}$-pump (SERCA2). $Ca^{2+}$-release from the SR for contraction primarily occurs via the ryanodine receptor channel (RYR).

substances are capable of preventing it, a 'summation hypothesis' has been proposed by Downey and colleagues.[31 36] In order for ischaemic preconditioning or pharmacological preconditioning to occur, it is necessary to reach an activation threshold. This threshold represents the sum of the activity of several mediators. The role of lactate as a triggering mechanism is controversial, even though lactate can open $K_{ATP}$ channels and increase the expression of heat-shock proteins.[4 65] Ischaemic preconditioning is caused by temporary occlusions, generally lasting 5 min, followed by reperfusion. A comparison of various numbers of cycles of ischaemia-reperfusion shows that protection is best with 1–4 cycles. With six or more cycles protection is reduced und ultimately lost.[47] While one cycle may be enough to trigger the release of protective substances, many more cycles may be unable to enhance further release of triggers. A high number of short ischaemic periods may start to cause cumulative ischaemic damage, thus decreasing the efficacy of preconditioning.[47]

Preconditioning reduces cardiomyocyte necrosis *in vivo* and *in vitro*. Apoptosis is known to increase with ischaemia.

In ischaemia-reperfusion, both ischaemia and reperfusion contribute equally to apoptosis.[76] By contrast, necrosis occurs primarily during reoxygenation. Preconditioning effectively reduces necrosis and apoptosis. Opening of $K_{ATP}$ channels together with modulation of $Ca^{2+}$ homeostasis may explain why inhalation anaesthetics inhibit apoptosis in cardiomyocytes.[3 151]

*Role of adenosine*

The role of adenosine in preconditioning has been well documented. Adenosine $A_1$-receptor activation plays an important role. These receptors are coupled with $K_{ATP}$ channels[68] via Gi-proteins. Activation of adenosine receptors decreases the production of reactive oxygen species and attenuates myocardial stunning.[92] The role of adenosine receptors in preconditioning is confirmed by the observation that adenosine $A_1$-receptor antagonists can block $K_{ATP}$ channels, thereby preventing ischaemic preconditioning. In addition, preconditioning can be mimicked by adenosine $A_1$-receptor agonists.

*Role of bradykinin*

Bradykinin is an inflammatory stress mediator and a vasodilator. In some experimental models, an infusion of bradykinin has been shown to reduce ischaemic injury,[15 36] while bradykinin receptor antagonists negated the protection conferred by ischaemic preconditioning.[15 36]

*Role of opioids*

Morphine and fentanyl have been shown to precondition the myocardium.[58 120 152] Conversely, δ-opioids receptor antagonists prevent ischaemic preconditioning.[84 122 123]

*Role of adrenergic receptors*

Both α- and β-adrenoceptors are involved in preconditioning. While preconditioning is induced primarily by $\beta_1$-adrenoceptors,[34] $\beta_2$-adrenoceptor may play a role via activation of L-type calcium channels. Brief episodes of ischaemia cause the release of norepinephrine in the myocardium, while exogenous $\alpha_1$-adrenoceptor agonists may cause pharmacological preconditioning.[132]

*Role of free oxygen radicals and nitric oxide*

Free radicals cause myocardial damage during ischaemia-reperfusion. However, treatment with small amounts of free radicals before an ischaemic insult can reduce infarct size *in vitro*,[6] an effect that is abolished by free radical scavengers. Nitric oxide-cGMP signalling is also important.[25 33 92 152] Inhalation anaesthetics may modulate the activity of various isoenzymes of nitric oxide synthase (nNOS, eNOS, iNOS) as they are heterogeneously distributed in the myocardium.

*Calcium ions*

A preischaemic increase in $Ca^{2+}$ represents a second messenger in the development of ischaemic preconditioning,[85] even though $Ca^{2+}$ overload is a major contributor to cell damage. Short-time administration of increased $Ca^{2+}$ concentrations to myocardial tissue is an effective preconditioning stimulus, which can be inhibited by administration of $Ca^{2+}$ channel blockers.[141]

*Protein kinase C (PKC)*

PKC transfers γ-phosphoryls from ATP to hydroxyl groups of serine/threonine residues in proteins. This phosphorylation controls the function of many cellular effectors. PKC plays an important role in ischaemic and pharmacological preconditioning.[50 113 134 139] PKC activators can induce, while PKC inhibitors prevent preconditioning.[150] Inhalation anaesthetics may directly activate PKC. Importantly, preconditioning-associated isoform translocation of PKC to subcellular targets is highly dependent on species, age, and on the type of preconditioning stimulus.

*Role of ATP-dependent potassium channels ($K_{ATP}$ channels)*

Ultimately, $K_{ATP}$ channels hold the central role in ischaemic and pharmacological preconditioning[153] (Figures 2 and 3). Sarcolemmal $K_{ATP}$ channels were described by Noma in 1983.[96] These channels open when ATP levels fall, allowing potassium efflux so causing membrane hyperpolarization and reducing the action potential duration. These changes decrease the open probability of voltage-gated $Ca^{2+}$ channels. The resulting reduction in $Ca^{2+}$ concentration preserves ATP levels and reduces coronary vascular tone.[118] The increase in extracellular potassium also facilitates coronary vasodilatation and increases blood flow to the ischaemic region.[5] $K_{ATP}$ channels mediate the response to hypoxia and the hyperaemic response to brief coronary occlusions. However, reduction of action potential duration does not correlate with the reduction in infarct size. Surface $K_{ATP}$ channels were initially thought to mediate preconditioning. More recent evidence indicates that mitochondrial $K_{ATP}$ channels play a pivotal role in mediating cardiac preconditioning.[35 153] Opening of mitochondrial $K_{ATP}$ channels may optimize mitochondrial energy production, decrease mitochondrial $Ca^{2+}$ overload, and prevent opening of mitochondrial permeability transition pores (Fig. 4).[30 43 83 157] Numerous studies have confirmed the important role of these channels. The role of $K_{ATP}$ channels in human preconditioning is evidenced by the observation that ischaemic preconditioning does not occur in patients taking sulfonylureas, as these agents block $K_{ATP}$ channels.[13 21]

*Other beneficial effects associated with cardiac preconditioning*

Glycogen depletion and lactate accumulation during ischaemic preconditioning periods play a role in myocardial protection. Indeed, transient exposure to lactate improves contractile recovery in rat heart.[29] Entrapment of neutrophils and platelets in the coronary vasculature occurs in ischaemia. The protective effects of preconditioning also extend to the endothelium of the coronary vasculature and to the adhesion properties of platelets and leucocytes to these vessels. Ischaemic preconditioning reduces ICAM-1 production and thus neutrophil entrapment.[116] In turn, reduced neutrophil and platelet entrapment is associated with enhanced post-ischaemic function.[44 45]

*Late preconditioning*

Late preconditioning is mediated by inducible nitric oxide synthase[129 146] and can be elicited by nitric oxide donors.[46 130] It can also be triggered by heat stress, lipopolysaccharides (LPS), or monophosphoryl lipid A; these are known to trigger delayed endogenous protective mechanisms against myocardial ischaemia-reperfusion injury appearing after 24 h and lasting for several days.[11] Alterations of gene expression of protective and anti-protective proteins along with $K_{ATP}$ channel opening have been proposed as the main mechanisms for this delayed protection. The endocannabinoid system is involved in the protection conferred by LPS, in relation with nitric oxide production.[74] Two endocannabinoids act through interaction with G-protein coupled membrane receptors, namely $CB_1$- and $CB_2$-receptors, which are present throughout the body.[103] Endocannabinoids have been implicated in the inflammatory response. In isolated rat hearts, endocannabinoids acting through $CB_2$-receptors and nitric oxide, play a role in the protection conferred by heat stress against myocardial ischaemia.[52] Hemin is an activator of the potent antioxidant enzyme heme oxygenase-1 and may play a role in delayed protection.[149] Enhanced expression of heme oxygenase-1 has been observed during the recovery phase of porcine myocardial stunning.[125] Indeed, in experimental studies, a significant attenuation of stunning, as evidenced by enhanced recovery of wall thickening was observed in animals pretreated for 1 week with hemin.[143] Whether inhalation anaesthetics are capable of eliciting late preconditioning is not yet clear.

*Remote preconditioning*

Ischaemic preconditioning can be generated by short episodes of myocardial, limb, or visceral ischaemia. In the heart itself, preconditioning can develop in areas remote from the preconditioning ischaemic stimulus (for review see[156]). This remote preconditioning may involve the release of adenosine, bradykinin, norepinephrine, and activation of $K_{ATP}$ channels. Systemic effects of localized ischaemic preconditioning have been reported. This raises the issue that regional ischaemia of non-vital tissues might protect remote vital organs.[37] In volunteers, transient remote ischaemia of one limb induced remote ischaemic preconditioning of the opposite limb as evidenced by preservation of endothelial function (estimated as extent of vasodilator response).[66] Cytokines and other metabolic mediators are likely to play a role. The autonomic system may also be involved as well as modulation of platelet, endothelium, and leucocyte function.

## Protective effects of anaesthetics against ischaemia

### *Anaesthetics and myocardial stunning*

Most inhalation anaesthetics and high dose opioids confer protection, increasing the rate of myocardial recovery after reperfusion.[58 115] In 1988, Warltier and colleagues[142] demonstrated that administration of halothane and isoflurane before ischaemia improved the speed of recovery of function after a brief (15 min) period of ischaemia. After 5 h, the functional recovery in the presence of inhalation anaesthesia was 100% *vs* 50% only in the controls.[142] Since then, these observations have been confirmed repeatedly.[22 134] However, some studies of isolated heart preparations showed no protection by inhalation anaesthetics.[97 117] More recently, sevoflurane and desflurane were shown to confer cardiac protection.[108 109 119 133 135] It is likely that protection by inhalation anaesthetics is attributable to pharmacological preconditioning of the heart, as in many studies the inhalational anaesthetic was given before ischaemia and reperfusion. Indeed, in some studies the administration of the inhalation anaesthetic was discontinued before ischaemia-reperfusion and resulted in reduced infarct size.[18 24] Nonetheless, protective effects of inhalation anesthetics were also reported if inhalation anaesthetics were administered exclusively during the reperfusion phase.

Intravenous anaesthetics appear to confer less protection.[23 27 144] Fentanyl and propofol appear to be equivalent.[114] In the isolated heart, as opposed to the intact instrumented heart, propofol has been shown to reduce infarct size and cellular damage.[70 71 82] Propofol-induced protection was not abolished by block of $K_{ATP}$ channels. While the effects of opioids on infarct size have been well demonstrated, there are only a few studies of their effects on myocardial stunning.[114 144] In the isolated heart, high concentrations of fentanyl have been shown to offer significant protection.[58] Protection was mediated by δ-opioid receptors, adenosine $A_1$-receptors, PKC, and $K_{ATP}$ channels.[56 57] The role of δ-opioid receptors is supported by the abolition of their protective effect by naloxone.[20 122 131] As wash-out of opioids does not prevent their effect, they must act as preconditioning agents.[2 75] It is further possible that opioids act beneficially via a reduction in adhesion and migration of neutrophils.[128 140]

### *Anaesthetics and cardiac preconditioning*

Many anaesthetic agents have been shown to reduce infarct size in experimental models. Not all anaesthetics have the same efficacy. There is greater reduction of infarct size by halothane, enflurane, and isoflurane in comparison with pentobarbital, ketamine-xylazine, or propofol anaesthesia in rabbits. Dogs anaesthetized with barbiturates exhibit larger infarcts than their conscious counterparts.[53] This may be

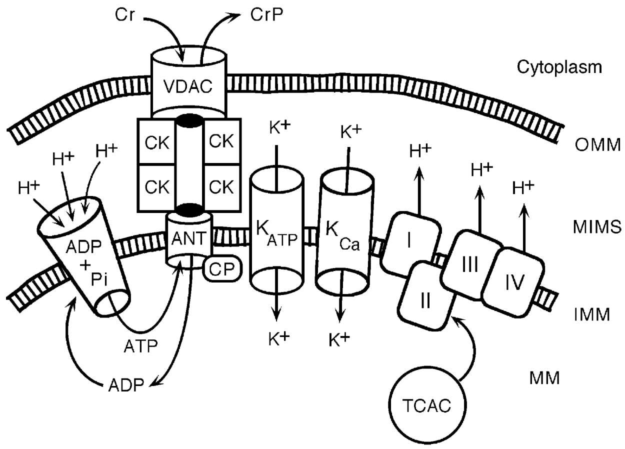


**Fig 4** Functional connections between the mitochondrial permeability transition pore (mPTP) and the oxidative energy production during ischaemia-reperfusion and pharmacological preconditioning (PC). The selective adenine nucleotide translocator (ANT) at the inner mitochondrial membrane (IMM) regulates ATP supply to the cytoplasm in exchange for ADP, which will be regenerated to ATP in the mitochondrial matrix (MM) by the ATP synthase (ADP + Pi). The synthase is driven by the proton gradient across the IMM. The high proton concentration in the intermembrane space (MIMS) is maintained by the respiratory chain complexes (I–IV), which are energetically fuelled by the tricarboxylic acid cycle (TCAC) in the MM. On its way out of the MM, ATP passes through the ANT and enters a channel formed by an octameric complex of the mitochondrial creatine kinase (CK) where its gamma-phosphoryl is transferred to creatine (Cr) to produce creatine phosphate (CrP), which leaves the mitochondrion through the voltage-dependent anion channel (VDAC or porin) in the outer membrane (OMM) into the cytoplasm. Wherever energy is required, transphosphorylation from CrP to local ADP yields ATP for immediate use. The Cr–CK system serves as energy shuttle between the production centre and the place of consumption. The VDAC allows solutes to pass up to a molecular weight of 5000 Da. The nucleotide conductivity of ANT is controlled by cyclophilin-D (CP) at its inner opening. Binding of $Ca^{2+}$ (which is increased during ischaemia-reperfusion) to CP induces ANT to form a non-selective channel for solutes up to a molecular weight of 1500 Da. Cyclosporin-A can bind to CP and prevents channel opening, while atractyloside binds to ANT itself and favours channel opening. During ischaemia cessation of ATP production produces a decrease of diffuse $K^+$ influx. Consequently, the MM shrinks somewhat at the expense of an increase of the MIMS leading to destabilization of the complex between ANT, CK and VDAC. On reperfusion additional ROS and $Ca^{2+}$ trigger opening of the ANT channel, which then seems to join directly to the VDAC forming a non-selective mega-pore, the mPTP. This leads to the collapse of the IMM potential, to massive MM swelling and disruption of the OMM. As $K^+$ acts as the main MM volume regulator, activation of $K^+$ influx represents the most powerful mechanism to prevent mitochondrial destabilization and therewith irreversible destruction and cell death. Both ischaemic and pharmacological PC activate the mitochondrial ATP-dependent potassium channels (mK-ATP) affording myocyte protection against ischaemia-reperfusion injury. In addition, a large conductance $Ca^{2+}$-activated potassium channel (K-Ca) known to exist in the surface membrane of vascular smooth muscle cells was also found in the MIM. This channel is regulated by physiological variations of cytosolic $Ca^{2+}$, and when selectively activated, it also protects the myocytes against ischaemia-reperfusion injury.[30 43 83 157]

explained by the observation that barbiturates competitively antagonize adenosine $A_1$-receptors, a pivotal signalling pathway in cardiac preconditioning. Indeed, adenosine receptor antagonists decrease anaesthesia-induced preconditioning.[24 113] The same is true of PKC antagonists.[134] Albeit not proven, it may be speculated that pharmacological preconditioning by inhalation anaesthetics may be of smaller magnitude than ischaemic preconditioning.[18]

Pharmacological preconditioning by inhalation anaesthetics appears to be primarily mediated by stimulation of adenosine receptors[113] and activation of $K_{ATP}$ channels.[62 113] Protective effects by inhalation anaesthetics also occur in the presence of cardioplegic protection. Ischaemic and anaesthetic-induced preconditioning are not additive suggesting the same end-effector,[12] identified in many studies as $K_{ATP}$ channels. Nonetheless, sevoflurane can potentiate late ischaemic preconditioning in an *in vivo* rabbit model.[87] The signalling components involved in cardiac protection by inhalational anaesthetics, are similar to ischaemic preconditioning, but show distinct differences.[26] Both sarcolemmal and mitochondrial $K_{ATP}$ channels may mediate anaesthesia-induced preconditioning as demonstrated in desflurane-mediated preconditioning.[135] Yet, mitochondrial $K_{ATP}$ channels may play the more important role. Halothane partially blocks sarcolemmal $K_{ATP}$ channels,[113] while isoflurane does not. Anaesthesia-induced preconditioning is clearly species dependent. Halothane preconditions in rabbit but not rat or human. Isoflurane preconditions in rabbit and human, but not rat (for review see[155 156]).

Anaesthetics may also modulate the effects of ischaemic preconditioning. Several anaesthetic agents have direct effects on $K_{ATP}$ channels (barbiturates) or have prominent physiological effects that are induced by $K_{ATP}$ channels (isoflurane, halothane).[17] Accordingly, ischaemic preconditioning is abolished by glibenclamide under ketamine-xylazine anaesthesia but not pentobarbital anaesthesia. In a comparison of the effects of ischaemic preconditioning under pentobarbital, isoflurane, and ketamine-xylazine anaesthesia, infarct size was not different in the absence of preconditioning, but the magnitude of infarct size limitation by ischaemic preconditioning was different depending upon the basal anaesthesia.[38] In the presence of halothane anaesthesia, nicorandil given before ischaemia did not demonstrate protective effects, whereas ischaemic preconditioning did reduce infarct size. Yet, a $K_{ATP}$ channel blocker prevented the combined effect of ischaemia and nicorandil.[90] The complexity of modulatory effects of anaesthetics on cardiac preconditioning has been substantiated in a cellular model of simulated ischaemia. Modulatory effects of anaesthetics were demonstrated by the inhibition of diazoxide-induced mitochondrial $K_{ATP}$ channel opening by R-ketamine, thiopental and pentobarbital. Conversely, urethane, 2,2,2-trichloroethanol (a main metabolite of α-chloralose) and fentanyl potentiated the channel-opening effect of diazoxide. This potentiation could be blocked by chelerythrine, a specific PKC inhibitor. By contrast, S-ketamine, propofol, xylazine, midazolam and etomidate do not affect mitochondrial $K_{ATP}$ channel activity.[152] These observations illustrate the complex interference of anaesthetics with ischaemic preconditioning and stress the concept of anaesthetics acting as modulators of cardiac preconditioning.

To date, there are few data on the possibility of inhalation anaesthetics conferring late preconditioning, whereas delayed protection by opioids is well established.[121] Kehl and colleagues[60] examined the effect of isoflurane administration 24 h before a 60 min coronary occlusion followed by 3 h reperfusion in a canine model. While isoflurane exerted early protection, there was no late protection. By contrast, delayed preconditioning was observed in a rabbit model.[137]

Finally, improved collateral blood flow may also play a role in the beneficial effects elicited by anaesthetics. Indeed, sevoflurane increases collateral flow, an effect not reversed by glibenclamide.[64] In addition, halothane, isoflurane, and sevoflurane reduce the number of neutrophils[45 73] and platelets[44] sequestered in the coronary vasculature after ischaemia. This may contribute to the observed beneficial effects. Inhalation anaesthetics further suppress the post-ischaemic expression of CD11b[45] and thus decrease neutrophil adhesion to the endothelium.[86] However, sevoflurane does not reduce the expression of glycoprotein IIb/IIIa, a platelet adhesion molecule involved in the platelet–endothelium interaction.[44]

*Isoflurane*

In the absence of ischaemia, isoflurane causes opening of $K_{ATP}$ channels, an effect blocked by sulfonylureas.[61] This results in a reduction in infarct size in experimental animals.[63] Isoflurane also decreases infarct size in an *in vitro* model of human myocardium.[113] Sarcolemmal and mitochondrial $K_{ATP}$ channels appear to be involved.[61 106 113 133 136] Isoflurane increases the open probability of the sarcoplasmic $K_{ATP}$ channel for a given ATP concentration.[39] In a cellular model, isoflurane significantly enhanced the diazoxide-mediated activation of mitochondrial $K_{ATP}$ channels. This effect was completely blocked by chelerythrine (a PKC inhibitor). Pretreatment with inhalation anaesthetics potentiated the diazoxide-mediated protection against ischaemia. Cardioprotection was unaffected by the sarcoplasmic $K_{ATP}$ channel blocker HMR-1098, but sensitive to modulation of nitric oxide and adenosine-Gi signalling pathways.[153] Administration of isoflurane before aortic cross-clamping in patients undergoing coronary artery bypass surgery causes cardiac index to be higher after cardiopulmonary bypass with less changes in ST-segments than in the control group. However, there were no differences in terms of arrhythmias.[42] Thus, isoflurane may offer some additional protection to cardioplegia. These findings are consistent with the observation of lower (albeit not statistically significant) perioperative levels of CK-MB and troponin reported by Belhomme[8] when isoflurane is used. Moreover, isoflurane was found to increase 5′-nucleotidase activity in atrial tissue indicating increased PKC activity.[8]

*Sevoflurane*

Sevoflurane reduces infarct size in dogs via opening of $K_{ATP}$ channels.[133] Preservation of myocardial blood flow through collateral circulation, observed with sevoflurane, is independent of $K_{ATP}$ channels. In sepsis, ultrastructural changes in the myocardium have been documented and sevoflurane protected cardiac output in septic (caecal ligation and perforation) rats.[124] Recently, the first clinical double-blinded multicentre study has shown sevoflurane to protect myocardium and kidney in patients undergoing coronary artery bypass grafting.[54] This study also visualized for the first time PKC translocation (predominantly isoforms δ and ε) to subcellular targets such as the sarcolemma, mitochondria, intercalated disks, and nuclei in response to sevoflurane. Moreover, the observed renoprotective effect of sevoflurane raises the intriguing possibility that systemically administered sevoflurane may confer multiorgan protection in high-risk patients.

*Desflurane*

In isolated human atrial trabeculae, desflurane improved the recovery of isometric contraction after a 30 min period of anoxia. The preconditioning effect of desflurane was abolished by glibenclamide, 5-hydroxydecanoate (5-HD), DPX (an adenosine receptor blocker), phentolamine, and propranolol.[41] These observations suggest that preconditioning by desflurane is mediated by mitochondrial $K_{ATP}$ channels,[41] adenosine $A_1$-receptors, and α- and β-adrenoceptors. In contrast, selective block of sarcolemmal $K_{ATP}$ channels did not reduce desflurane-induced preconditioning, while it abolished anoxia-induced preconditioning. Desflurane increases sympathetic activity in volunteers and releases catecholamines from myocardial stores in rat and human myocardium.[40] Preconditioning by desflurane may thus be, at least partly, elicited by stimulation of the α/β-adrenoceptor pathways.[77]

## Pharmacological interventions by nonanaesthetic agents currently used for the prevention of perioperative ischaemia

Several classes of drugs have been proposed in order to reduce the risk of ischaemic complications of anaesthesia and surgery. However, based on current clinical data, only beta-blockers, $\alpha_2$-adrenoceptor agonists, and possibly statins may have the potential to affect perioperative cardiovascular outcome.

*Nitroglycerin*

While nitroglycerin is used successfully in the treatment of myocardial ischaemia, there is no evidence that its prophylactic administration before anaesthesia and surgery decreases the risk of perioperative cardiac complications.[127]

*Calcium channel blockers*

Though effective in the management of ischaemic heart disease, $Ca^{2+}$ channel blockers have never been shown to offer any protection against perioperative cardiac complications of anaesthesia and surgery.[126 127] This absence of protection seems surprising in view of the strong antioxidant effect of certain calcium channel blockers.[147]

*Adenosine modulators*
These compounds facilitate the release of the coronary vasodilator adenosine by the ischaemic myocardium, thereby improving collateral blood flow toward the compromised area. Though promising results were obtained,[80] development of the only agent tested in clinical trials, acadesine, was stopped.

*$\alpha_2$-Adrenoceptor agonists*
There is renewed interest in the use of clonidine, dexmedetomidine, and (temporarily, as it is not currently being further developed for clinical use) mivazerol; these drugs reduce the level of sympathetic activity and make the circulation more stable. Clonidine decreases the risk of perioperative myocardial ischaemia[95] and a recent meta-analysis has also shown a reduction in the risk of adverse outcome.[127] Mivazerol has been tested in a large multicentre trial and was shown to decrease the incidence of cardiac complications in vascular surgical patients but not in non-vascular surgical patients,[98] yet its development was stopped.

*Nicorandil*
This drug is both a nitrate and a $K_{ATP}$ channel opener. It is effective in the management of ischaemic heart disease and its associated dysrhythmias. It may prove useful in the perioperative prevention of cardiac complications.[55] In clinical practice, nicorandil, a $K_{ATP}$ channel opener and nitrate, is widely used in the treatment of angina. Nicorandil induces myocardial preconditioning. In isolated human heart muscle nicorandil conferred cardioprotection (improved recovery of function in a hypoxia-reoxygenation model). This effect was abolished by ischaemic preconditioning.[16] In a rabbit model early treatment with nicorandil (pre-ischaemia) decreased infarct size, while nicorandil administration after ischaemia was ineffective. Ischaemic preconditioning reduced infarct size and the combination of ischaemic preconditioning and nicorandil showed efficacy intermediate between ischaemic preconditioning and before administration of nicorandil.[49] The effect of nicorandil was blocked by 5-hydroxydecanoate, a $K_{ATP}$ channel blocker. Thus, nicorandil appears to protect by opening $K_{ATP}$ channels, and to interact with ischaemic preconditioning. By contrast, nicorandil appears to offer additional protection when administered with isoflurane, in terms of functional recovery of the stunned myocardium.[105]

*Statins*
In a case-controlled study, Poldermans and colleagues[107] evaluated the effects of statins on perioperative mortality in patients undergoing major vascular surgery. In statin-treated patients, the risk for perioperative mortality was ~20% of that observed in non-statin-treated patients. The authors concluded that perioperative statin use may reduce perioperative mortality in high-risk vascular patients.

*$\beta$-Blockers*
These drugs, at present, occupy centre stage for cardiac prophylaxis because several studies have shown a reduction in the incidence of cardiac complications of anaesthesia and surgery in patients deliberately given beta-blockers prophylactically.[154] The beneficial effects of perioperative β-blocker administration are discussed in detail in another article in this issue.

## Conclusions

Myocardial ischaemic injury is a potential perioperative threat. Ischaemia induces a palette of myocardial states with distinct pathophysiological backgrounds ranging from the paradoxically beneficial effects of preconditioning on one side to the complete loss of cellular integrity and to cell death on the other side. Preconditioning mimicking agents such as inhalation anaesthetics and opioids induce a pronounced protective cardiac phenotype and thus may decrease, along with β-blockers, $\alpha_2$-adrenoceptor agonists, and anti-inflammatory/preconditioning-mimicking statins, the deleterious effects of myocardial ischaemia in perioperative medicine.

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